Application of Monte Carlo Methods in Molecular Targeted Radionuclide Therapy

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SUMMARY

Targeted radionuclide therapy promises to expand the role of radiation beyond the treatment of localized tumors. This novel form of therapy targets metastatic cancers by combining radioactive isotopes with tumor-seeking molecules such as monoclonal antibodies and custom-designed synthetic agents. Ultimately, like conventional radiotherapy, the effectiveness of targeted radionuclide therapy is limited by the maximum dose that can be given to a critical, normal tissue, such as bone marrow, kidneys, and lungs.

Because radionuclide therapy relies on biological delivery of radiation, its optimization and characterization are necessarily different than for conventional radiation therapy. We have initiated the development of a new, Monte Carlo transport-based treatment planning system for molecular targeted radiation therapy as part of the MINERVA treatment planning system. This system calculates patient-specific radiation dose estimates using a set of computed tomography scans to describe the 3D patient anatomy, combined with 2D (planar image) and 3D (SPECT, or single photon emission computed tomography) to describe the time-dependent radiation source. The accuracy of such a dose calculation is limited primarily by the accuracy of the initial radiation source distribution, overlaid on the patient's anatomy.

This presentation provides an overview of MINERVA functionality for molecular targeted radiation therapy, and describes early validation and implementation results of Monte Carlo simulations.

I. BACKGROUND

Over the last several decades, radiation has proven to be highly effective in the treatment of cancer. Currently, radiation is used to treat about half of all cancer patients, via collimated beams and encapsulated internal sources. However, these physical delivery methods are limited to the treatment of localized cancer, often at the primary site of occurrence.

The development of new, highly specific molecular targeting agents means that radiation can now be delivered directly to cancer cells using the body's own distribution system as the delivery mechanism, thus allowing for control of widespread cancer. Recent clinical results point to the promise of this novel form of cancer therapy.[1]

The benefits of and state-of-the-art for treatment planning have been described by several authors.[2, 3, 4] In general, there are two key treatment planning challenges: optimizing drug administration and predicting in advance how much the patient will benefit from the therapy.

A new treatment planning system, MINERVA is being developed to support a broad range of modern radiation therapy methods, where the name MINERVA stands for Modality-INclusive Environment for Radiotherapeutic Variable Analysis.[5] This presentation describes the requirements, design and initial testing of the MINERVA photon-electron Monte Carlo transport system for molecular targeted radiation therapy.

II. TREATMENT PLANNING FOR MOLECULAR TARGETED RADIATION THERAPY

In the treatment planning process, a diagnostic test dose of radiolabeled drug is used to acquire serial 2- and 3-D maps of radioisotope concentration in the patient. The treatment planning system overlays this information onto a model of the patient's anatomy to calculate the corresponding radiation dose to tumor(s) and normal organs.

To support this functionality, the treatment planning system must: (1) allow the user to describe the anatomical composition of the patient; (2) provide a mechanism to input serial digital maps of radioisotope concentrations, taken from standard nuclear medicine imaging systems; (3) combine radiosotope measurements made at sequential times with mono- or bi-exponential functions, in order to develop a time-integrated, organ-specific and, ideally, 3-D characterization of activity; (4) map the time-integrated activity onto the patient's anatomy; (5) simulate the resulting radiation dose; (6) report the radiation dose to tumors and important normal organs.

Radioisotope distributions are obtained from either planar (2D) or SPECT (3D) images, examples of which are shown in Figures 1 and 2. Both imaging techniques present their own advantages and disadvantages. Planar images are relatively easy to obtain, and are the workhorse of radioisotope localization. However, it is not always possible to sort out multiple
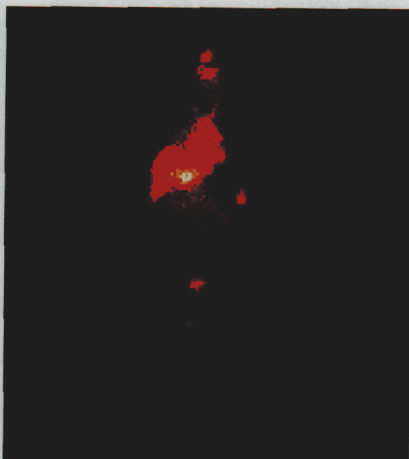

Figure 1. Anterior planar image of a prostate cancer patient treated with molecular targeted radiation

sources that are located at different depths in the patient. SPECT images provide 3D information, but are more time consuming to collect, and have a fairly poor resolution. In both cases, correction for scatter and attenuation are important considerations, and are accounted for by a variety of techniques.[6]

In an ideal world, it would be possible to fuse SPECT images onto a patient's CT scan to obtain a voxel-by-voxel representation of activity in the patient. And, with new CT/SPECT scanners, this possibility is nearing reality. However, this level of sophistication is not practical in most targeted radionuclide clinical
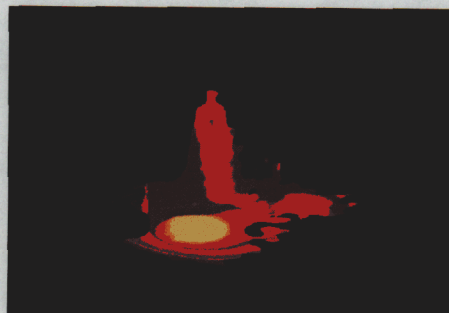

Figure 2. Coronal and sagittal views of fused SPECT and CT images of a breast cancer patient treated with molecular targeted radiation therapy.

settings due to an array of hardware and logistical considerations. The more practical current solution, which MINERVA will support in its initial configuration, is to assign a uniform activity to each organ and tumor volume visualized on the patient's CT scan, where these activities are taken from region-of-interest analysis of radionuclide scans. This enables the treatment planning system to use the patient's own anatomy for radiation absorbed dose calculations, while avoiding potential mis-registration of activity due to patient motion, patient repositioning, and the relatively low (7-10 mm) resolution of radionuclide detection system. Coupled with 3D Monte Carlo simulations, this approach represents a substantial advance over MIRD standard-man system.[7, 8]

II. PHOTON-ELECTRON RADIATION TRANSPORT

The photon-electron Monte Carlo transport system in MINERVA is based on the PEREGRINE code,[9] and simulates a molecular targeted radiation treatment as follows: the code samples photons and electrons from a 3D, time-integrated activity map generated from the treatment planning system, using the radionuclide emission energies and branching ratios; then, photons, electrons and their progeny are tracked through the patient using random numbers and microscopic particle-interaction probabilities. As each particle interacts, it sets in motion other particles that are also tracked; and the code sums each particle's contribution to the radiation absorbed dose.

Atomic data and transport methods used in our codes system described in detail elsewhere.[9] Photons are tracked using standard analog methods. Secondary photons created below 10 keV were not tracked and the minimum photon tracking energy was 100 eV for photons that arise as a result of Compton collisions.

The class-II condensed history method is used for charged particle transport,[10] modeling knock-on and bremsstrahlung processes above specified cut-off energies as discrete events. The Moliére[11] multiple scattering method is employed, implemented as in the EGS4 code. Electron step sizes and deflection-angle algorithms are determined as described in Reference 9.

Unrestricted electron stopping powers are calculated from the formulas described in ICRU Report 37.[12] The implementation for sampling knock-on events of Møller scattering (for electrons) and Bhabha scattering (for positrons) is the same as for the EGS4 code.[13] The bremsstrahlung cross sections and emitted photon spectral data were obtained from the Lawrence Livermore National Laboratory's Evaluated Electron Data Library (EEDL).[14] We used a 20 keV bremsstrahlung creation threshold, 20 keV kinetic energy knock-on electron creation threshold, and 10 keV kinetic energy electron tracking cut off.

All simulations were done in a 0.5x0.5x0.5 m³, unit-density cube with a tissue composition used by Stabin and Konijnenberg.[15] Sources were uniformly distributed in homogeneous spheres located at the center of the cube, and energy collection was done in these spheres. All simulations were done with 1 million histories, to a standard deviation < 1.2 %.

IV. VALIDATION STUDIES

Although the Monte Carlo simulation algorithms used here have been extensively validated for external beam photon therapy,[9, 16] this is their first application to internal radiation sources.

Most targeted radionuclide therapy uses gamma-rays to determine radioisotope localization, while beta particles are primarily responsible for depositing dose locally. Therefore, accurate tracking of both particle types is important for both radiation transport and dose estimation. Our validation approach is to compare MINERVA simulations with: (1) MCNP and EGS4 simulations for monoenergetic photon and electron point sources, (2) MCNP and EGS4 simulations for commonly-used isotope point sources, and (3) MIRD

anthropomorphic phantom results for important target and source organs.

Here we report the results of the first step of the validation process. Figures 3 and 4 compare MINERVA simulation results with photon and electron absorbed fractions recommended by Ref. 15, which are averages of EGS4 and MCNP.

Figure 3 shows the agreement between MINERVA and recommended values for photon energies ranging from 20 keV to 2.75 MeV. For 20-40 keV photon sources, MINERVA absorbed fraction results are systematically lower than the recommended values in Ref.15. Differences are greatest for low energies, within 6% at 20-40 keV, and within 3% for higher energies. For all energies and volumes, MINERVA and EGS4 (reported in Ref. 15) agree to within 3%. For energies less than or equal to 662 keV and sphere masses less than 60 g, MINERVA, EGS4, and MCNP predict absorbed fractions that are 20-40% higher than MIRD 8.[17] At 2.75
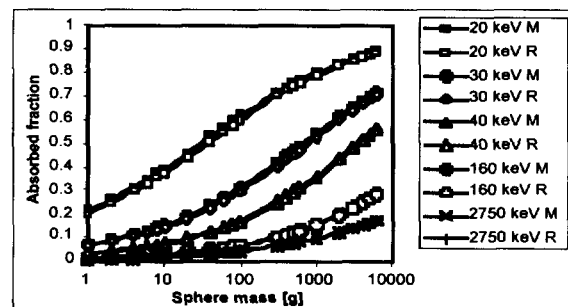
Figure 3. Comparison between photon absorbed fractions for MINERVA (M) and Ref. 15 (R).

MeV, all three codes predict absorbed fractions that are 10-50% lower than MIRD 8.

Figure 4 shows the agreement between MINERVA and recommended values for electron energies ranging from 20 keV to 4 MeV. Here, our results are systematically lower than absorbed fractions recommended in Ref. 15 for
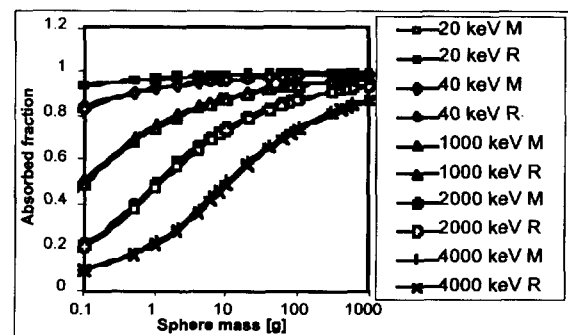
Figure 4. Comparison between photon absorbed fractions for MINERVA (M) and Ref. 15 (R).

high energies and small volumes: for spherical masses greater than 1 g and energies at and below 2 MeV, MINERVA agrees with recommended values to within 2%. At 4 MeV, up to 5% differences are found. However, MINERVA agrees with EGS4 to within 1.5%. For 0.1-1 g sphere sizes and energies at and above 700 keV, MINERVA disagrees with the recommended values by as much as 8%, but agrees with EGS4 to within 2%. Discrepancies reflect the difference between the MCNP and EGS4 results reported in Ref. 15, and likely result from differences in electron transport algorithms between MINERVA / EGS4 and MCNP, and in energy threshold and cut-off.

VII. CONCLUSIONS

Treatment planning for molecular targeted radiation therapy enables the physician to estimate the radiation absorbed dose delivered to the patient based on time-dependent radiosotope maps and patient anatomy. This presentation provides an overview of MINERVA functionality for targeted radionuclide therapy and describes early validation and implementation results of Monte Carlo simulations.

In order to support the accurate simulation of radiation dose from internally-distributed radioisotopes, we have modified the PEREGRINE Monte Carlo dose calculation code to simulate dose from internal radioemitters. As an initial step in the validation of this system, we have compared calculated absorbed fractions to those obtained by EGS4 and MCNP for photon and electron point sources with energies ranging from 20 keV to 4 MeV. All three codes agree to within 5% for most cases, and, for small-mass spheres, predict substantially different photon absorbed fractions than MIRD 8.

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